

# Apremilast and Systemic Retinoid Combination Treatment for Moderate to Severe Palmoplantar Psoriasis

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## PRACTICE POINTS

- Palmoplantar psoriasis is challenging to treat and is unresponsive to many modalities.
- Combination, rotational, and sequential treatment approaches may minimize side effects and loss of efficacy as well as enhance treatment responses.
- Apremilast and acitretin combination therapy led to 90% skin improvement in a case of severe recalcitrant palmoplantar psoriasis.

To the Editor:

Psoriasis is a chronic inflammatory papulosquamous skin disease affecting 2% to 3% of the population.<sup>1</sup> Its pathogenesis is multifactorial, consisting of a disrupted skin barrier and dysregulated immune activation.<sup>2</sup>

A wide armamentarium of topical and systemic treatments targeting different aspects of the disease pathogenesis have been developed over the years.<sup>3,4</sup> Psoriasis was once considered a skin disease exclusively, but

accumulating evidence suggests that it is accompanied by a multitude of systemic inflammatory comorbidities.<sup>5</sup> This insight supports the concept of systemic treatment for patients with moderate to severe psoriasis. As a chronic disease, psoriasis requires continuous therapy. The treatment approach should focus on achieving efficacy and minimizing side effects. These goals can be achieved by combination, rotational, and sequential treatment approaches.<sup>6</sup> Many therapeutic combinations have proven effective, using beneficially different mechanisms of action (MOAs) and toxicity profiles.<sup>7</sup> We present a patient with moderate to severe recalcitrant palmoplantar psoriasis who demonstrated improvement with combination therapy.

A 50-year-old man presented with palmoplantar psoriasis of 7 years' duration. His medical history included mild hyperlipidemia treated with atorvastatin. Prior topical treatments including calcipotriene, betamethasone dipropionate, and tacrolimus ointment did not result in improvement. Persistent acral involvement required further intervention, and the excimer laser was added to the therapeutic regimen with a minor additive therapeutic

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value. Acitretin (25 mg/d) was initiated; however, the disease flared up soon after. Acitretin was discontinued, and the patient was treated with apremilast (30 mg twice daily) for 9 months with a slight improvement. Physical examination revealed erythematous, fissured, scaly plaques involving both the palms and soles. Acitretin (25 mg/d) was reintroduced to the therapeutic regimen, and the acitretin-apremilast combination was used for 2 months. With this regimen, the patient experienced 90% improvement (Figures 1 and 2).

Palmoplantar psoriasis is a debilitating dermatosis that is extremely challenging to treat and is unresponsive to many modalities.<sup>8</sup> Increased understanding of psoriasis mechanisms paved the path for the development of highly targeted biologic therapies<sup>9</sup> with fewer side effects than drugs such as cyclosporine that indiscriminately neutralize multiple components of the immune system. Although highly specific, these targeted approaches are not without side effects<sup>10</sup> and lead to diverse therapeutic outcomes, particularly when prescribed for palmoplantar psoriasis.<sup>11,12</sup>

The small-molecule inhibitor of phosphodiesterase 4—apremilast—was approved for plaque psoriasis treatment in late 2014. Although not fully elucidated, its MOA involves interfering with intracellular signaling, leading to increased intracellular cyclic adenosine monophosphate levels in inflammatory cells and keratinocytes.<sup>13</sup>

Proximal interruption of the pathologic cascade leads to the reduction of multiple proinflammatory cytokines with a simultaneous increase in anti-inflammatory mediators.<sup>13</sup> Its efficacy and safety in the treatment of psoriasis have been shown in phase 2 and 3 clinical trials.<sup>14,15</sup> In contrast to traditional oral therapies for psoriasis (ie, methotrexate, cyclosporine, acitretin), no laboratory test monitoring is needed and the safety profile is notably better.<sup>16</sup>

Acitretin, the active metabolite of etretinate, modulates epidermal differentiation and has immunomodulating activities.<sup>17</sup> It commonly is used for treating palmoplantar psoriasis.<sup>8</sup> Until recently, it was the only nonimmunosuppressive systemic treatment for psoriasis, and its combination with other systemic treatments, particularly biologics, has been advocated.<sup>18</sup> Prior reports showed remarkable disease improvement when combining acitretin with alefacept, etanercept, infliximab, adalimumab, and ustekinumab.<sup>19</sup> The optimal combination should include modalities with different MOAs without overlapping toxicities.<sup>19</sup> Apremilast and acitretin have different MOAs and side-effect profiles, but another theoretical advantage is that they both interfere with intracellular signaling on the transcription level rather than affecting extracellular targets.<sup>13</sup>

Our patient with moderate to severe recalcitrant palmoplantar psoriasis demonstrated approximately 90% improvement following apremilast and acitretin combination therapy.



**FIGURE 1.** A, Palmoplantar psoriasis plaques before therapy. B, The palms cleared following acitretin and apremilast combination treatment.



**FIGURE 2.** A, Psoriasis plaques involving the dorsal aspect of the right hand before therapy. B, The plaque and thumb fingernail improved following acitretin and apremilast combination treatment.

This treatment regimen should be considered in cases of persistent acral disease resistant to other therapeutic efforts.

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